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The spatial configuration of chromatin is fundamental to ensure any given cell can fulfil its functional duties, from gene expression to specialised cellular division. Significant technological innovations have facilitated further insights into the structure, function and regulation of three-dimensional chromatin organisation. To date the vast majority of investigations into chromatin organisation have been conducted in interphase and mitotic cells leaving meiotic chromatin relatively unexplored. In combination, cytological and genome-wide contact frequency analyses in mammalian germ cells have recently demonstrated that large-scale chromatin structures in meiotic prophase I are reminiscent of the sequential loop arrays found in mitotic cells, although interphase-like segmentation of transcriptionally active and inactive regions are also evident along the length of chromosomes. Here, we discuss the similarities and differences of such large-scale chromatin architecture, between interphase, mitotic and meiotic cells, as well as their functional relevance and the proposed modulatory mechanisms which underlie them.

Interphase Chromatin Organisation

To date the most comprehensive characterisations of chromatin architecture have been conducted in interphase cells producing a wealth of knowledge to describe the hierarchical organisation of chromatin spanning from a linear genetic sequence to complex chromatin networks. The hierarchical organisation of mammalian chromatin in interphase begins with a highly flexible chromatin fibre where the DNA has been wrapped around 11-nm octameric histone cores and combined with linker histones to form nucleosomal units (1). Chromatin is decorated by multiple layers of regulatory adaptations including DNA methylation and hydroxymethylation (2), post-translational modifications of exposed histone tails (3) and the binding of chromatin remodellers (4) and chromatin-associated RNAs (5,6). As a consequence of such modifications chromatin fibres begin to fold and when viewed by electron microscopy (EM) and other biophysical techniques often appear to be approximately 30-nm in diameter *in vitro* (7). Intriguingly, emerging evidence has begun to question the existence of a 30-nm fibre *in vivo*, for instance near-native state cryo-EM studies failed to detect 30-nm fibres but instead reported the presence of disordered fibres 5-24 nm in diameter (8–12). Despite being under scrutiny such chromatin fibres are thought to be the fundamental basis from which large-scale chromatin structures are built.

Significant use of chromosome conformation capture (3C) technologies, including genome-wide HiC and capture-3C, has led to recent advances in chromatin mapping beyond the 30-nm fibre in interphase cells (13). This suite of technological approaches, which enables the 3D proximity of genomic loci to be assessed by quantifying the likelihood that two loci physically interact with one

another, has revealed that entire chromosomes are compartmentalised into chromatin loops and topologically associated domains (TADs) (14). Chromatin loops form when stretches of chromatin positioned in *cis* are more likely to specifically interact with one another than with their intervening sequences (15), these interactions are highly dynamic and possess a predicted life-span of up to ten minutes in mammals (16). TADs are 3C-defined self-associating chromatin regions, within which the chromatin exhibits a preferential interaction bias. In mouse embryonic stem cells TADs extend for a median of 880 kb (17). Although fluorescent in situ hybridisation (FISH) has shown that intra-TAD loci experience a two- to three-fold rise in physical proximity compared to inter-TAD loci (17), it is not clear how chromatin is physically arranged within and between TADs.

Accumulating evidence suggests that both interphase TADs and chromatin loops have a functional role in the regulation of transcription. Gene regulatory elements can be positioned several hundred kilobases from their affiliated genes (18,19) however, capture-3C and HiC experiments have demonstrated that promoters and their regulatory elements are held in close physical proximity (18). Detailed characterisation of the *β-globin* locus has demonstrated that artificial tethering of the transcription factor, LDB1, mediates formation of a chromatin loop between the gene's promoter and its locus control region, which consequently results in the recruitment of RNA polymerase II and the up-regulation of *β-globin* transcription (20). These findings point towards a role for specific chromatin looping interactions in promoting gene expression at some genomic loci however, HiC investigations have revealed that approximately 50% of human promoters do not specifically interact at chromatin loop anchor sites (15). Nevertheless, most promoter-regulatory element interactions are confined to a common TAD leading to fewer than 10% of such interactions violating TAD boundaries (21,22). This suggests that the intra-domain proximity facilitated by individual TADs might be involved in regulating gene expression or that some specific interactions are transient and therefore may be indistinguishable at the resolution of current 3C analyses. The physical isolation of individual TADs has also been shown to prevent ectopic contacts forming between non-specific regulatory elements and promoters, meaning disruption of inter-TAD insulation can result in gene mis-expression and deleterious phenotypic outcomes (23,24). In one instance, loss of insulation between two neighbouring TADs led to a constitutive enhancer aberrantly interacting with the oncogenic *Pdgfra* gene, causing a 3-fold rise in *Pdgfra* expression and a 2-fold growth advantage in a glioma cell line (23).

In addition to TAD and chromatin loops, larger structures, referred to as chromosome compartments and nuclear territories, have also been identified in interphase cells. The arrangement of both chromosome compartments and nuclear territories within the nucleus appear to correlate with the transcriptional activity. Compartments are chromosomal regions of similar transcriptional activity that coalesce in close nuclear proximity. 3C analyses tend to categorise nuclear compartments into two, A and B, which correspond to transcriptionally active, largely euchromatic and inactive, largely heterochromatic chromatin, respectively (15,25,26). A and B compartments have a strong correlation with nuclear positioning as A-type chromatin locates within the nuclear interior whilst B-type chromatin is present nearer to the nuclear envelope (27). Basic thermodynamics of polymer chains predicts a preferential bias towards *cis*, rather than *trans*, interactions and 3C investigation have confirmed these predictions, highlighting the physical individualisation of chromosomes within the interphase nucleus (25). Extensive FISH experiments have demonstrated that individual chromosomes are not randomly organised within the nucleus and occupy chromosome territories that exhibit preferential positioning relative to the nuclear centre. This radial positioning of chromosomes correlates with transcriptional activity, as again those near the nuclear periphery are repressed and those in the nuclear centre are active (28,29). The mechanisms by which chromosome compartments and territories are assembled and maintained is not clear. Investigations have demonstrated that

transcriptional activity and the state of chromatin condensation can directly dictate gene repositioning within the nucleus (30) however, further insight is required to produce a complete functional model for chromatin clustering within the interphase nucleus.

The Chromatin Loop Extrusion Model

Chromatin loop extrusion is a dynamic model which postulates how mapped chromatin loops and TADs form (Fig. 1). The model suggests that loop extrusion factors (LEFs) physically bind two adjacent genomic regions, whereupon the intervening chromatin fibre is extruded as the LEF actively or passively translocates away from its loading origin, consequently holding together increasingly more genetically distal sequences. Extrusion halts when the LEF becomes displaced from the chromatin or its movement is stalled by immobile boundary elements (31). The loop extrusion model describes how individual chromatin loops can form however, it has been proposed that multiple chromatin loops could work in concert to generate individual TADs (32). Importantly, the creation and maintenance of chromatin loops, as defined by the loop extrusion model, is highly plastic and dynamic as extrusion factors and boundary elements continually associate and dissociate (16).

Evidence to substantiate the loop extrusion model has largely been generated from genome-wide 3C experiments, which have enabled interphase TADs and loops to be defined in a range of conditions. Polymer simulations based on the predicted kinetics of LEFs and boundary elements, as well as the biophysical properties of chromatin, have accurately recapitulated genome-wide TAD and chromatin loop maps produced experimentally (32–34). These simulations were also able to accurately predict interaction maps produced following the deletion of boundary regions (22) and targeted disruption of boundary elements (33,35–38). In addition real-time imaging of λ-DNA in combination with candidate LEFs has produced convincing visual evidence for the formation and processive extrusion of DNA loops, thus complementing *in silico* findings (39).

It is important to acknowledge that alternative mechanisms to the loop extrusion model can also explain the formation of large-scale chromatin structures. For instance, the simplest alternative model describes how a ‘stepping motor’, such as condensin, compacts chromatin fibres as chromatin is drawn together to generate a loop when the motor ‘steps’ and progresses along the fibre. Therefore the extent of extrusion imposed on DNA by a motor is dependent on chromatin fibre tension. This model is comparable to the loop extrusion model however, it is not reliant on two loci being bridged at any one time (40).

Interphase Loop Extrusion

LEFs are integral to the loop extrusion model by creating a scaffold through which a chromatin fibre is passed and extruded. The best characterised and most favoured LEFs in somatic cells are members of the structural maintenance of chromosome (SMC) protein family. The SMC protein family is highly conserved and is an important group of proteins which in vertebrates include cohesin, condensin and the Smc5/6 complex (41). Eukaryotic SMC proteins act in SMC homo- and heterodimers with specialised non-SMC proteins to create multi-protein complexes which are capable of entrapping chromatin fibres (42). It is not clear whether Smc5/6 complexes act as a LEF in this context, since the complexes have principally been shown to participate in DNA repair pathways and the modulation of genome stability (43). However, cohesin and condensin are involved in the manipulation of large-scale chromatin architecture and are both strongly implicated as LEFs (42,44).

While condensin is implicated in LEF activity in mitosis (refer to 'Large-scale chromatin organisation in mitosis'), emerging evidence has demonstrated that cohesin is a good candidate as a LEF during interphase. Mammalian cohesin in somatic cells is composed of two SMC family members, SMC1α and SMC3, a kleisin protein RAD21, and a stromal antigen group, either SA1 or SA2 (42). The cohesin subunits form rings which are capable of topologically entrapping chromatin and provide the primary mechanism to maintain sister chromatid cohesion, until their timely bipolar segregation at the metaphase-to-anaphase transition during mitosis (45,46). Studies utilising cohesin chromatin immunoprecipitation (ChIP) and HiC data in interphase cells have demonstrated that cohesin is enriched at the base of chromatin loops and at TAD boundaries (15,17,25). Cohesin is capable of physically bringing genetically distal loci positioned in *cis* into closer physical proximity, by either a single cohesin ring simultaneously embracing two stretches of chromatin or cohesin rings dimerising to form handcuffs, in which each monomer constrains a single chromatin region (47). Notably, *in vitro* single-molecule imaging has confirmed that cohesin can migrate in an ATP-dependent manner along chromatin fibres from its site of loading until it dissociates from the chromatin or a specific obstacle impedes its route, as would be expected of a LEF (48,49). Although cohesin has the capacity to migrate independently of other mechanisms the action of RNA polymerase has been proposed to promote its migration (50). This proposal is substantiated in *S. pombe* where transcription diverges from the centre of TADs causing TAD boundaries and cohesin-enriched sites to colocalise with points of convergent transcription (51). These findings were mirrored in the human genome where cohesin accumulated at sites of convergent transcription however, this was only detected in the absence of the candidate boundary element CTCF and Wapl, a cohesin release factor (52).

Artificial manipulation of cohesin abundance, both positively and negatively, results in drastic changes in chromatin loop length (53–55). For instance, auxin-induced degradation (AID) of the AID-tagged cohesin subunit RAD21 eliminates the vast majority of loop domains defined by high-resolution HiC and polymer modelling (53). Additionally, deletion of the cohesin release factor *Wapl,* results in the extension of longer chromatin loops with a median increase of 200kb (54), indicating that cohesin has an important role in the formation and/or maintenance of chromatin loops (56).

The loop extrusion model is not only dependent on LEFs but also boundaries. CTCF is a highly conserved architectural protein that binds to thousands of sites throughout the mammalian genome in a sequence-specific manner through its high-affinity zinc finger array (57). In human cells CTCF co-localises with TAD boundaries and loop contact points and is proposed to stabilise chromatin loops by acting as a boundary element (32,33,58). The acute depletion of functional CTCF genome-wide results in the loss of chromatin looping between CTCF sites and causes contiguous TADs to merge together (24,59). Consistently, removal of specific CTCF sites abolishes CTCF-binding, interferes with cohesin recruitment and again perturbs the distribution of chromatin loops and TADs (33,36). ChIP studies have also found that cohesin is heavily enriched at CTCF sites, for instance in HeLa cells 89% of cohesin binding sites (as defined by RAD21 ChIP) co-localise with CTCF sites across the genome (60). In the context of the loop extrusion model the spatial relationship between cohesin and CTCF can be explained as the mobility of the LEF, cohesin, is interrupted by the canonical boundary element, CTCF. Such a proposition is reinforced by *in vitro* single-molecule imaging which indicates that the diffusion of cohesin along DNA can be impeded by CTCF binding (48,49).

Interestingly, the number of CTCF binding motifs are in excess of the number required to create the full repertoire of chromatin loops presently defined in a range of cell types. This apparent inconsistency can be explained by HiC mapping which has demonstrated that chromatin looping preferentially occurs between pairs of high affinity (61) CTCF-binding sites orientated in a convergent configuration at chromatin loop anchor points (15). In support of this model, the binding affinity of

CTCF, and to varying degrees cohesin, is not disrupted by the artificial re-orientation of convergent CTCF motifs into divergent or tandem alignments, yet long-range chromatin loop structures are abnormally arranged (33,35,36). However, a number of instances have been discovered in which the positioning and/or orientation of CTCF motifs do not conform to those predicted from chromatin loop mapping. For instance, a significant fraction of loop and TADs boundaries have been shown to align with tandem (62) or divergent CTCF sites (63). Furthermore, the underlying mechanisms responsible for dynamically manipulating CTCF binding, including the role of epigenetic marks (64) or CTCF-RNA binding, still require further elucidation (65,66).

Large-Scale Chromatin Organisation in Mitosis

Mitosis is delineated by one round of DNA replication, duplicating each chromosome into two sister chromatids, followed by a single round of nuclear division segregating sister chromatids from one another to generate two daughter cells with a similar DNA content to each other and to their parent. During eukaryotic mitosis, chromosomes are more highly condensed than in interphase, presumably to facilitate the alignment and movement of chromosomes on the mitotic spindles and their faithful segregation into the daughter cell (67–70). Recent studies estimate that metaphase chromatin is compacted 10-fold more than within the average interphase nucleus (71) to approximately 150 $Mb/\mu m^3$ (72). Unsurprisingly, in order to attain such an extreme level of compaction the manner by which mitotic chromatin is organised is highly distinct from interphase chromosomes (69,73). 3C analyses indicate that interphase-associated compartments and TADs disappear within 10 minutes of release from a G_2 block (69,74,75). In order for the chromatin to become sufficiently compacted in mitosis the linear chromatin fibre of each chromatid adopts a morphology much akin to a bottlebrush in which the chromatin forms consecutive loop arrays with each loop extending approximately 80-120 kb according to both HiC (74) and EM analyses (72,76). The bottlebrush configuration is particularly evident at pericentromeric chromatin, which has been shown to establish the spring-like tension at centromeres required for the faithful sister chromatid separation during mitosis (77–79). As a consequence of chromatin loop array formation chromosomes undergo longitudinal compaction until metaphase is reached and each chromosome has adopted a helical coil configuration (72,74). Early structural analyses utilising strategies such as transmission EM highlighted mitotic chromatin loop arrays emanate from a central, discontinuous scaffold (76,80) composed primarily of condensin and topoisomerase II alpha (81). Over 95% of mitotic loops are not positioned at sequence-specific sites and thus are thought to attach randomly to the core axis to form a chromatin network with great inter-cellular heterogeneity (74).

Mitotic Loop Extrusion

Although cohesin and CTCF are regarded as highly important in the orchestration of large-scale chromatin structures in interphase cells it is thought mitotic systems are largely independent of these structural components. Indeed, cohesin is depleted from the chromosome arms during mitotic prophase, then completely removed from the chromosomes at the metaphase-anaphase transition to enable sister chromatid segregation (82,83). In addition, mapping of CTCF binding using antibody-targeted MNase activity to release CTCF-DNA complexes for DNA sequencing demonstrated that CTCF

is largely lost from mitotic chromatin (75). This removal may be due to the phosphorylation of CTCF's linker domains (84–86), which *in vitro* significantly reduces the binding capacity of CTCF (87,88).

Instead, much attention has focussed on understanding the formation of condensin-mediated chromatin loops in mitosis (58,74,89). Condensin is a second representative of the SMC protein complex family (90,91) and has two variants, condensin I and condensin II, both of which are composed of five constituent subunits, including SMC2 and SMC4 (90). Similarly to cohesin, condensin has the capacity to topologically link DNA duplexes (92) and has DNA translocase activity (93), producing a means by which condensin may migrate relative to DNA and facilitate loop extrusion. To substantiate condensin as a LEF, studies have captured condensin-dependent loop extrusion via real-time imaging (39), whilst coarse-grained simulations have accurately recapitulated condensin-mediated loop extrusion in a mitotic context (34). Furthermore, *in vitro* investigations have also shown that condensin in combination with topoisomerase II, core histones, and three histone chaperones are capable of fully reconstituting mitotic chromatids (81). Artificial ablation of both condensin I and II complexes *in vivo* causes mitotic chromatin to exhibit interphase-like 3D configurations and promotes the creation of tetraploid daughter cells (74,94). This therefore suggests that disruption of interphase-associated TAD and chromatin loop structures and the generation of mitotic chromatin loop arrays are reliant on the presence of condensin complexes.

Meiosis and Meiotic Recombination

During gametogenesis, cells as well as their constituent chromatin, experience alterations that ultimately enable the generation of gametes. Meiosis commences with a round of DNA replication that duplicates each chromosomes into two sister chromatids. However in contrast to mitosis, this round of DNA replication is followed by two rounds of nuclear division that first separates the two homologous copies of each chromosome, then their constituent sister chromatids. The haploid daughter cells that arise from meiosis therefore contain half the number of chromosomes that their diploid progenitors possessed, which maintains the ploidy of sexually reproducing species (95). Prior to the first meiotic division the genome undergoes a highly specialised process in prophase I, referred to as meiotic recombination (96,97). Meiotic recombination begins with the formation of hundreds of programmed double strand breaks (DSBs) throughout the genome that are enriched at specific sites known as meiotic hotspots (98–100). These intentional lesions are subsequently repaired by exploiting either the sister-chromatid or homologous chromosome as a reparative template (97,101). In a fraction of instances (~10% in mice) (101) the resolution of meiotic DSBs facilitates crossovers (COs), where the flanking DNA sequences are reciprocally exchanged between the maternally- and paternally-derived homologous chromosomes (102). As a consequence, COs promote genetic diversification, via the creation of novel allelic combinations, which can influence the direction of evolutionary change within a population (103). Additionally, COs also facilitate physical connections between homologous chromosomes called chiasmata, which are critical to ensure the faithful segregation of homologs in the first meiotic division (95).

Large-Scale Chromatin Architecture in Meiotic Prophase I

The functional activity of cells during meiotic prophase I is highly distinct from those observed in mitosis or interphase. It is therefore likely that meiotic chromosomes are arranged distinctly in order to allow and spatially regulate the generation and repair of hundreds of DSBs, CO frequency and

distribution and the search/pairing of homologous chromosomes. It is important to note that within interphase cells large-scale chromatin organisation is frequently defined as structures above a 30-nm fibre (56). However, the existence of the 30-nm fibre in meiocytes has yet to be verified therefore presently we define large-scale chromatin structures as those which exhibit analogous features to large-scale structures in somatic cells. Cytological (104) and more recently HiC (105–108) analyses have demonstrated that large-scale chromatin architecture undergoes significant alterations as early as meiotic prophase I; from historic EM images it is evident that prophase I chromatin is not a simple linear fibre lacking any organisational strategy but is instead folded into orderly sets of sequential loop arrays (104), forming a structure reminiscent of a mitotic bottlebrush. Predictions from FISH conducted in mouse chromosome spreads suggest that these meiotic loops extend approximately 500 kb (109).

In meiotic prophase I telomeres cluster at the nuclear envelope, which leads to the polarisation of chromosomes in a 'bouquet' arrangement and the disruption of discrete chromosome territories. On binding to force-generating machinery at the nuclear periphery the chromosomes are subject to rapid chromosome movements, which have been attributed to pairing and subsequent synapsis of homologous chromosomes on their release from the nuclear envelope (110,111).

The specificity of inter-homolog interactions and synapsis is dependent on meiotic recombination, during which recombinase enzymes invade intact DNA duplexes in order to conduct a homology search and identify a homologous sequence available for homolog-mediated repair (112). Inter-homolog synapsis is unique to meiosis and is conferred in most mammals by a meiosis-specific complex, known as the synaptonemal complex (SC). The SC is a highly ordered structure composed of axial/lateral elements (AEs/LEs), transverse filaments (TFs) and a central element (CE) (Fig. 2) (113). The assembly of the SC is constrained by the temporal advances of meiotic prophase I, which is broken down into four cytologically distinct substages; leptotene, zygotene, pachytene and diplotene. In mammals the assembly of the SC initiates in leptotene as the AE components SYCP2 and SYCP3 begin to oligomerise (114,115) and assemble along a cohesin-based axis from which the chromatin fibre extends in sequential loop arrays. Oligomerisation of SYCP2 and SYCP3 continues until a single AE axis runs along the entire length of each chromosome. In zygotene homologous chromosomes undergo synapsis as the TF SYCP1 draws the homologous axes together in a zip-like manner. Synapsis and full SC assembly is completed in pachytene once the entirety of each chromosomes' axis (referred to as the lateral element (LE) within the context of each SC) is tethered to its homologous counterpart to produce an inter-axis distance of approximately 100 nm in mice (116). The SC becomes further stabilised by the loading of CE proteins SYCE1, SYCE2, SYCE3 and TEX12 (117–119). Notably, recent super-resolution microscopy investigations in *D. melanogaster* have highlighted that the SC is composed of two layers that are suggested to connect two non-sister chromatids between homologs (120). In addition, studies in *C. elegans* (121,122) and mice (123) have indicated that SC components are mobile and interact weakly, causing the SC composition and organisation to be dynamic. As meiocytes enter diplotene cyclin-dependent and aurora kinases work to promote the disassembly of the SC and desynapsis of homologous chromosomes, causing the physical links between homologous chromosomes to be largely disbanded with the exception of the CO sites (124).

Sequential chromatin loops can be visualised emanating from the SC during pachytene stages of meiosis (104). The SC appears to play a role in organising these loop arrays as mutations in the SC component SYCP3 cause the length of the SC to double, and the length of the loops to halve (125,126). SYCP3 is capable of directly interacting with double-stranded DNA, in addition to SC proteins. (127). *In vitro* single-molecule analysis has demonstrated that SYCP3 tetramers coordinate linkage between distinct DNA regions, bringing genetically distal loci into greater physical proximity (128). It is possible

that clusters of SYCP3 tetramers may therefore assist in the nucleation of chromatin loop structures through this genetic 'bridging' between distal loci to encourage SC compaction. Accordingly, HiC analysis in *S. cerevisiae* found that depletion of the AE protein ZIP1 promotes chromosome compaction, causing the interaction range of loci to be reduced (107).

Meiotic chromatin loop arrays are most thoroughly annotated in the *S. cerevisiae* genome and were originally mapped by a ChIP assay that isolated chromatin interacting with a yeast AE protein. This investigation demonstrated that in *S. cerevisiae* chromatin associates with the chromosome axis in a sequence-specific manner enabling axis-associated and loop-associated chromatin to be distinguished. These patterns have latterly been confirmed by HiC analyses in pachytene-enriched *S. cerevisiae*, which have mapped loop-like chromatin interactions and have enabled variables such as chromosome arm compaction to be quantified (107). In addition, the HiC data showed that meiotic looping has a strong dependency on cohesin binding and given that cohesin binding sites in yeast are highly reproducible this may explain the ability of prior ChIP experiments (129) to identify axis-associated chromatin sites.

In contrast to yeast, attempts to isolate and sequence SC-associated chromatin in mammals through ChIP for the AE protein SYCP3 (130) have not resulted in the enrichment of unique genomic sequences. Rather, repetitive sequences, principally including active SINE retrotransposons, were reported to be modestly enriched in the SYCP3 ChIP from both rodent and primate spermatocytes (130). The mammalian ChIP data also resonates with findings generated when nucleases were used to trim away peripheral loop-associated chromatin enabling the residual axis-proximal chromatin to be isolated and sequenced (113,131,132). Interestingly, active SINE elements are enriched for CTCF binding motifs (133) suggesting that, if present, CTCF may act as boundary element at these mapped SC-chromatin interactions sites. A number of transgenic mouse experiments have also shown that 'foreign' bacterial sequences inserted within the immunoglobulin locus do not visibly co-localise with the murine SC and consequently are forced to appear as loops anchored to the SC by endogenous chromatin (134,135). However, it is not yet clear if there is a specific sequence or genomic feature, such as a particular arrangement of SINE elements, within the immunoglobulin region that is responsible for this property.

It is only in recent months that HiC maps have successfully been reported in mouse (106,108,136) and Rhesus monkey (136) spermatocytes in prophase I. These HiC investigations revealed that as mammalian spermatocytes progress through prophase I interphase-defined TAD and compartment structures are lost and by pachytene smaller, more refined compartments (106,108,136), which extend up to 0.5-2 Mb (106), are apparent. A marked loss of long-range interactions exceeding 3-10 Mb was also observed in mouse spermatocytes (106,108), which supports the concept that meiotic chromatin is organised around a chromosome axis. The chromosome compartments defined in mammalian meiocytes are distinct from the reproducible loop-like structures mapped in yeast however, it is not known whether these differences reflect fundamental differences in the way that meiotic chromatin is organised and interacts with the SC between these species, or that interactions between meiotic chromatin and the SC exhibit more inter-cellular heterogeneity in mammals compared to yeast. It is important to also note that the potential of inter-sister and inter-homolog interactions being captured by 3C methodologies can complicate the identification of chromatin interactions occurring in *cis.*

The Function of Meiotic Chromatin Loop Arrays

The organisation of large-scale chromatin architecture in prophase I meiocytes has been attributed to a role in the global modulation of meiotic recombination and CO frequency (eg. Kauppi et al. 2011; Gruhn et al. 2013; Heng et al. 1996). One key piece of evidence to substantiate this proposal is that the frequency of MLH1 foci, a marker of COs, is more closely associated with the length of the SC than DSB marker frequency (140). SC length is in turn associated with the distance that chromosome paints extend away from the chromosome axis, which act as a proxy for loop length in pachytene (140). This correlation between CO frequency and chromatin organisation has not been observed in isolation, for instance CO frequency is known to be sexually dimorphic (141,142) and appears to scale with SC length; in both mouse (143) and human (144) females the SC is twice as long and CO abundance is two-fold greater than in their male counterparts. FISH data has also demonstrated that autosomal chromatin extends away from the axis to a lesser degree in human females than males (138,145), thus indicating that chromatin loops may be shorter in females than their males counterparts. Furthermore, an additional correlation between CO frequency and chromosome morphology has been observed at the mouse pseudoautosomal region (PAR), which is the short region of homology, spanning approximately 700 kb, between the heteromorphic sex chromosomes in male spermatocytes (146). In male mice CO frequency is approximately 7-fold higher at regions in the PAR than in females (147). The elevated CO rate at the male PAR has been proposed to be caused by the length of the SC being extended 4-fold per Mb of DNA, and chromatin-SC extensions shortening 3-7 fold relative to the autosomes, resulting in a ~10-20-fold increase in the frequency of DSB markers in this region (137,148).

Taken together these observations indicate that axis/SC length and/or chromatin loop length, may play a part in the global and regional modulation of CO abundance. However, it is important to highlight that this interpretation is based on measurements of SC and chromatin loop length in pachytene cells, where SC assembly is complete and, at least for autosomes, meiotic recombination has long since commenced. This therefore presents a temporal disparity between the observed chromosome organisation and presumably the mechanisms which determine early recombination levels. Reassuringly, when comparing human male and female chromatin organisation via FISH, the marked sex-specific differences in pachytene chromatin organisation correlated with observations made in leptotene (138), at which point meiotic recombination is initiated and the AEs begin to oligomerise.

Chromatin Loop Extrusion in Meiotic Prophase I

Meiotic Cohesin

During meiotic prophase I the canonical cohesin subunits SMC1α, SMC3 and RAD21 are supplemented with three meiosis-specific cohesin subunits, SMC1β, a paralog of SMC1α, and two kleisins, RAD21L and REC8, whilst SA1 and SA2 are replaced by STAG3, a third stromal antigen protein (149). These additional subunits associate with the canonical cohesin subunits to create an enhanced range of cohesin complexes available to meiocytes. Similarly, to somatic cells cohesin is essential for facilitating sister chromatid cohesion in meiocytes, which in turn is integral to CO formation and balanced meiotic segregation (150–152). In prophase I cohesin is also involved in the orchestration of gross chromosomal structure, particularly concerning the assembly of chromosome axes and the SC.

Throughout prophase I the two most prominent kleisin proteins are REC8 and RAD21L (153,154). In *Rec8-Rad21l* double mutant murine meiocytes are incapable of assembling AE proteins into

chromosome axes (155–157). Less severe axial aberrations are observed in single knockout mice; in male mice axes partially or completely depleted of *Rec8* are shortened (158,159). Furthermore, within meiocytes SMC1β is the more abundant of the two SMC1 paralogs and upon its removal mouse spermatocytes and oocytes experience a two-fold reduction in SC length (160). Notably, by placing the *Smc1α* gene under the control of a transgenic *Smc1β* promoter in *Smc1β*-/- spermatocytes a partial rescue in SC length is observed demonstrating a degree of redundancy between the SMC1 paralogs in the determination of SC length (161). The reduction in SC length in *Smc1β*-/- oocytes is accompanied by alterations in chromatin organisation as the length of chromatin extensions from the SC to appear highly heterogeneous relative to wildtype chromatin topology (160); Novak *et al.* postulate this is due to specific regions of chromatin being anchored to the SC by either SMC1β-dependent or -independent mechanisms, therefore only a subset of chromatin loop attachment sites along the chromosome axis are affected in *Smc1β*-/- spermatocytes causing a portion of 'anchored' chromatin to be released into loop domains (160).

Although the contribution of cohesin to chromatin loop structures in meiosis is not yet clear in mammals HiC analyses conducted in *S.cerevisiae* has demonstrated that as prophase I progresses there is a simultaneous rise in REC8-binding site contact frequencies (107) that appear to promote the generation of short, loop-like chromatin interactions during pachytene. Studies in *S.cerevisiae* have also shown that convergent transcription focuses chromatin-axis association sites in a cohesin-dependent manner (162). This indicates that similarly to interphase cells meiotic transcription machinery can manipulate large-scale chromatin organisation over long distances. These findings are complemented by HiC investigations in mouse (106,108,136) and *Rhesus macaque* (136) spermatocytes which demonstrated that the loci present within HiC-defined 'refined compartments' correspond with sites of active transcription.

Meiotic CTCF

CTCF has an undoubtable role in the assembly of the majority of interphase chromatin loops and TADs (59) however, CTCF is dispensable to long-range chromatin contact domains in numerous organisms including yeast and *C. elegans* (163,164) and during mammalian mitosis (75). Therefore the question of whether meiotic chromatin loop formation acts in a CTCF-dependent or -independent manner now stands. Meiotic recombination, SC formation and cohesin localisation in *Ctcf* knock-out mice all remain grossly unperturbed during meiotic prophase I (165). Furthermore, immunostaining for CTCF during meiotic prophase I shows the protein as a diffuse cloud covering the entire nucleus with a growing intensity over the sex chromosomes as prophase I progresses (165). This distribution indicates that CTCF does not preferentially localise at the chromosomes axes/SC, where one might assume it to reside if it were indeed a boundary element at the base of chromatin loops. Combined, these data suggest that the global formation of meiotic loops occurs independently of CTCF during meiotic prophase I, possibly in a manner analogous to that observed in mitotic cells. It is however interesting to note that putative meiotic loop anchor points, mapped by the positioning of specific histone marks and meiotic recombination-associated methyltransferase PRDM9, are significantly enriched for a subset of CTCF consensus motifs (Grey et al. 2017). It may therefore prove useful to assess direct CTCF-chromatin binding profiles as cells progress from a pre-meiotic state through to early prophase I.

Interestingly, a duplication of the canonical *Ctcf* gene has led to the creation of *Ctcfl* (or *Boris*), a paralog of *Ctcf* whose normal expression is restricted to the male germline (167). The role of CTCFL in relation to large-scale chromatin organisation is not presently understood, since the two paralogs

have evolved overlapping but distinct binding specificities and protein interactomes (168,169). CTCFL is predominantly expressed in spermatogonia and pre-leptotene spermatocytes, but has not been detected in prophase I spermatocytes (168,169). *Ctcfl*-null male mice exhibit a mild fertility defect characterised by aberrations in post-meiotic stages of spermatogenesis (168,170). Therefore, there is currently no published evidence to support that either CTCF or CTCFL have a direct influence on large-scale chromatin organisation during mouse meiotic prophase I however, it is possible they may influence such structures prior to entry in prophase I or by acting in a redundant manner.

Meiotic Condensin

Considering the morphological similarities of large-scale chromatin structures between mitotic and meiotic prophase I chromosomes it is possible that the condensin-mediated chromosomal rearrangements are conserved between cell states. However, compared to mitotic systems far less is known about the role of condensin complexes in meiotic cells. Studies in *S. cerevisiae* (171) and *C. elegans* (172,173) have shown that chromosome SC length, SC assembly and meiotic DSB repair fate are reliant on the presence and activity of condensin complexes, for instance both organisms experienced up to a 50% increase in SC length in the absence of specific condensin variants. Conditional deletion of condensin I and II in growing mouse oocytes from the end of the first meiotic prophase results in metaphase I chromosomes acquiring morphogenic abnormalities causing chromosomes to appear fuzzier and thicker, with more significant deformations in condensin II-deficient mice (174). These findings are consistent with condensin I and condensin II having a role in metaphase chromosome condensation, as has been observed in mitosis. However, the role of condensin in mammalian prophase I is not known.

Concluding remarks

In combination, cytological and recent HiC analyses have led to advances in the elucidation of large-scale chromatin structures in mammalian meiotic prophase I. Of particular note, is the resemblance of chromosome organisation in mitosis and meiotic prophase I, where sequential chromatin loop arrays emanating from a central axis have been observed. However, although mitotic chromosomes are devoid of TADs and chromosome compartments, attenuated versions of interphase-like compartments are evident within meiotic prophase I cells. Therefore, meiotic chromatin is distinctly organised but retains features consistent with both interphase and mitotic chromosomes. Such features are likely to be due to the chromatin being highly organised by the meiotic chromosome axis and SC, in order to influence inter-homolog synapsis and meiotic recombination, whilst coordinating ongoing transcription. How such compartment-like structures, defined by 3C analyses, correspond to the cytologically visible chromatin loop arrays in mammalian meiotic prophase I is not yet clear since the distribution of SC components and cohesin have not been definitively determined.

It is interesting to consider the structural features which underlie the chromatin in meiotic prophase I; it is possible that similar mechanisms, such as loop extrusion, are conserved with those found in interphase and mitotic systems. However, evidence suggests these are likely to be executed in a meiosis-specific manner, where cohesin subunits and SC components unique to meiosis are at play. Therefore, examining the direct relationship between these structural components and large-scale chromatin structures can provide new insight into their functional relationships. This will in turn

improve our understanding of the interplay between large-scale chromatin organisation and key meiotic events, including synapsis, meiotic recombination and CO in meiotic prophase I.

Abbreviations

AE, axial element; CO, crossover; DSB, double-strand bread; EM, electron microscopy; LE, lateral element; LEF, loop extrusion factor; SC, synaptonemal complex; SMC, structural maintenance of chromosome; TF, transverse filament; 3C, chromosome conformation capture.

Funding

Work in the authors' laboratories is supported by the Medical Research Council.

Acknowledgements

We thank James Crichton for critical reading of the manuscript.

Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

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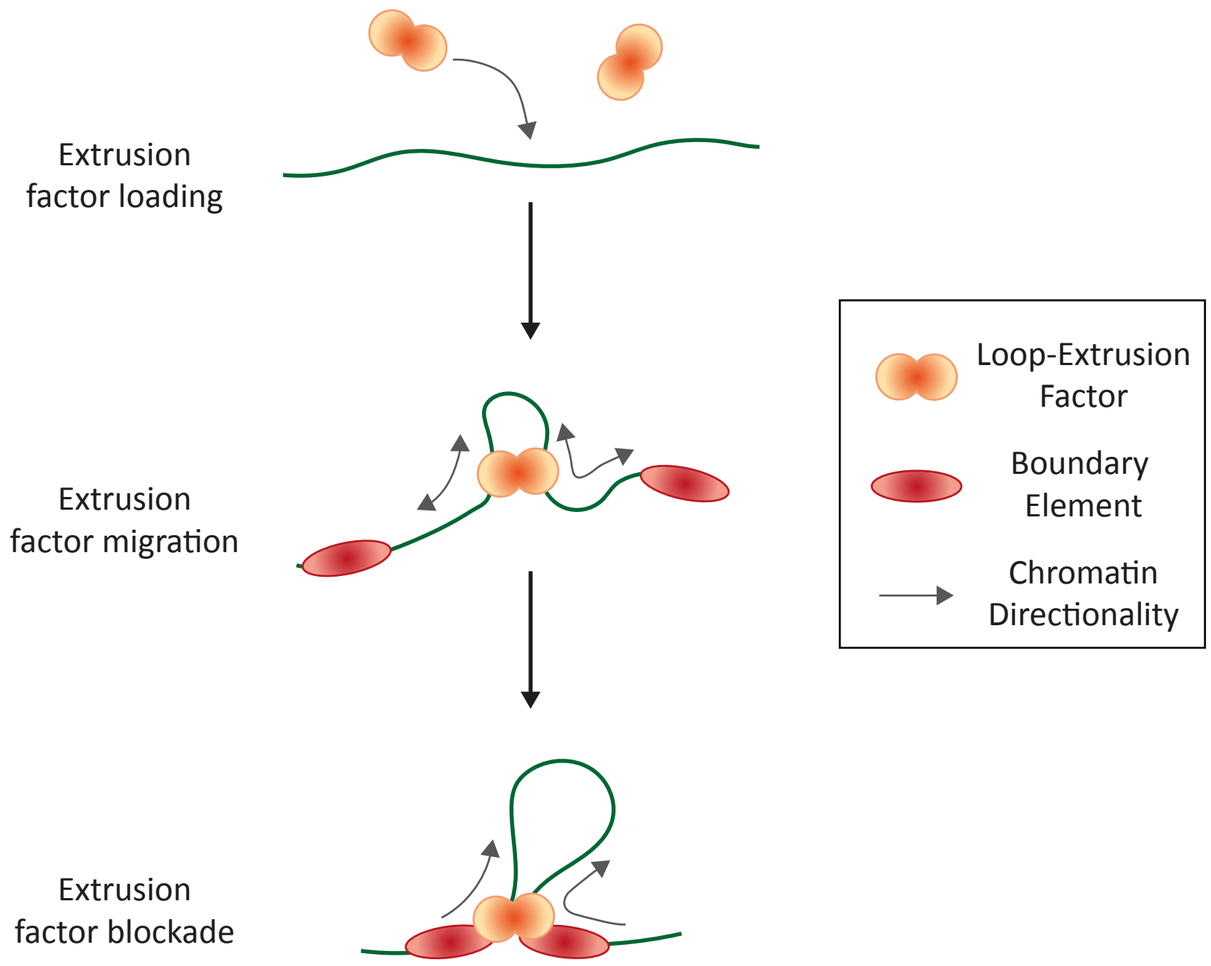

Figure 1. The Chromatin Loop Extrusion Model. A bivalent loop-extrusion factor is loaded onto chromatin and topologically entraps two chromatin sites. The extrusion factor then migrates along the chromatin, causing the intervening genomic distance between the two sites bound by the loop-extrusion factor to grow linearly in time. Ultimately, extrusion is impeded by the presence of a boundary element creating an extrusion factor blockade.

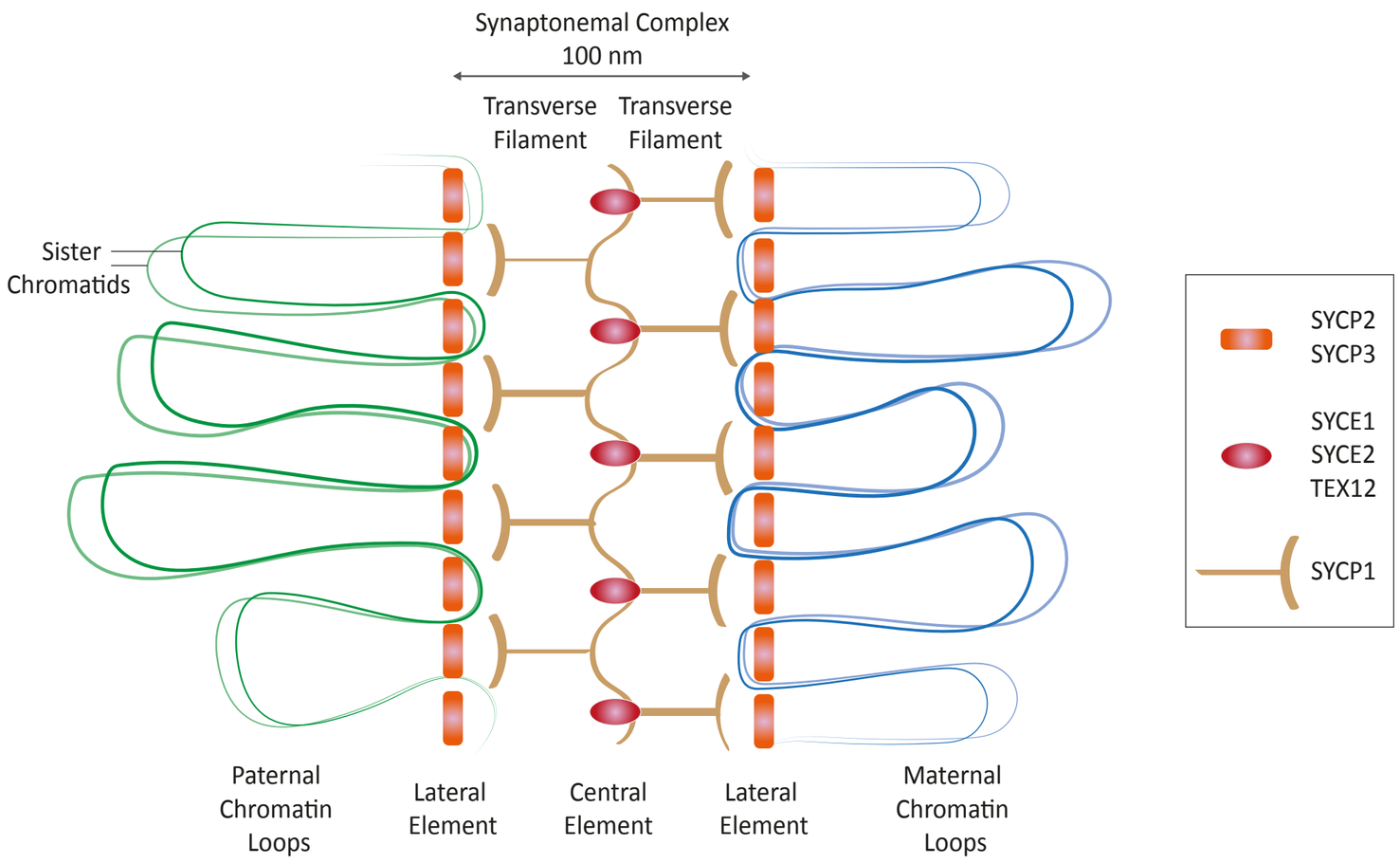

Figure 2. Organisation of the Synaptonemal Complex. Meiotic chromosomes are organised into a sequential chromatin loop arrays, the base of which associates with a highly proteinaceous structure referred to as the synaptonemal complex (SC). The SC is a tripartite structure composed of lateral elements (SYCP2 and SYCP3) that run the length of each chromosome and transverse filaments (SYCP1) that tether homologous chromosomes to one another whilst central elements (SYCE1, SYCE2 and TEX12) stabilise the SC.